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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,457	03/12/2001	Michael P. Maher	AUROBIO.026A	8759

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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,457	MAHER ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 02 February 2004.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-29, 49 and 50 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-29, 49-50 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

DETAILED ACTION

Formal Matters

Claims 1-29, 49-50 are pending and under consideration.

Response to Amendment

Applicant's arguments filed 2/2/2004 have been fully considered but they are not persuasive for the reasons set forth below.

The Objection to the Specification is withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-21 stand rejected, and new claim 49 is rejected, under 35 U.S.C. 102(b) as being anticipated by Sinha et al. (1995), for reasons of record set forth in the Office Action of 10/02/2003.

The rejection of record stated that Sinha et al. developed a system for simultaneous optical recording of transients of membrane potential and intracellular calcium concentration from mammalian brain slice preparations with high spatio-temporal resolution. In the method of Sinha et al. simultaneous recording was achieved by using two dedicated photodetectors together with two fluorescent indicators. Specifically, the calcium-sensitive dye Calcium Orange and the voltage-sensitive dye RH-414 were used because they have overlapping excitation spectra, but separable emission spectra. The method of Sinha et al. anticipates claims 1 and 21 because the

method uses cells (specifically, hippocampal slices, see page 53), the cells are exposed to a compound (the glutamate antagonists CNQX and d-APV, see page 56, Figure 5), and the cells are exposed to an electric field without using a patch clamp (in this instance a single stimulus is delivered via an electrode to the stratum radiatum area. N.b. this is not a patch clamp set-up since the electrode is a tungsten stimulation electrode and is used to induce an electric field potential which induces the cellular response, but does not make use of the patch clamp technique wherein a glass pipette filled with a solution which contains ionic salts is in contact with the interior of the cell.). The method of Sinha also measures transmembrane potential without using the patch clamp technique because the cells are loaded with dyes sensitive to transmembrane potential, and the fluorescence is measured (see page 56, Figure 5), thus claims 1, 2 and 21 are anticipated. Claims 3 and 4 are anticipated because the current pulses will not cause electroporation, claims 5-10 are anticipated because the cells comprise a voltage gated ion channel which will be released from inactivation in response to the stimulation, and the measuring was done using a transmembrane potential dye. Claims 11-20 are anticipated because the responses are stimulated with 500 micro sec current pulses delivered at frequencies less than 0.05 Hz (page 53, column 2, last paragraph).

Applicant has amended the claims by adding the limitations wherein the cells are exposed to two or more electric fields, and wherein the Tm changes in a single direction away from the starting Tm. Applicant argues that this form of Tm change is not disclosed or suggested by any of the prior art of record. However, the Sinha reference teaches that for recording evoked responses 500 microsecond paired current pulses were used (page 53, second column, last line on the page), thus meeting the limitation wherein a series of two or more electric fields are applied.

Additionally, it is an inherent property of the Tm to change in a single direction away from the starting Tm. In the hippocampal cells taught in Sinha, the Tm of the cells, in response to the paired pulse would rise from the resting Tm (expected to be slightly positive of the potassium equilibrium potential) to the sodium equilibrium potential (i.e. a Tm change in a single direction), and then back towards the potassium equilibrium potential as the sodium channels inactivated. Claim 49 is anticipated because the paired pulse electric field will maintain the Tm within the predefined range, if only for 500 microseconds. Thus the claims are still anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-29 stand rejected, and new claim 50 is rejected, under 35 U.S.C. 103(a) as being unpatentable over WO 96/41166 (Tsien et al.), for reasons of record set forth in the Office Action of 10/02/2003.

Tsien et al. teaches methods of assaying for small changes in transmembrane potential using voltage sensitive dyes (page 3, lines 1-25). Tsien et al. teach methods of screening for potential therapeutic drugs that affect membrane potentials in living cells (page 42). Tsien et al. further teach the use of cells which have been transfected with nucleic acids encoding, *inter alia*, ion channels (page 44, lines 1-5). Tsien et al. further teaches the use of cell lines including HEK293, LM(TK-), COS, and CHO cells (page 44, lines 7-11). Tsien et al. teaches that the transfected cells are treated with a stimulus that modulates the ion channel (page 43, lines 15-20). Tsien et al. teaches that the ion channel may be a sodium, potassium, or calcium channel, which may be voltage-gated (page 43, lines 27-31). While Tsien et al. does not set forth the stimulation protocols, it is a designer's choice to use an electric field to stimulate the ion channel, given that it is known in the art to use electric fields to stimulate voltage gated ion channels, as shown in Jacobs et al. Jacobs et al. teaches the electric field stimulation of cultured cells to stimulate Ca⁺⁺ transients (see page 4130, column 1, second paragraph and page 4131, Figure 1). Thus it would have been obvious to one of skill in the art at the time the invention was made to practice a method of assaying a compound agent for activity against an ion channel wherein a cell line is transfected with the ion channel of interest, and the cells are activated with an electric field, and the transmembrane potential is measured without the use of a patch clamp. The motivation is provided in the Tsien et al. reference that teaches that the method is sensitive to

small changes in transmembrane potentials, and can respond on a rapid, millisecond timescale to changes in membrane potentials (page 2, lines 30-38).

Applicant has amended the claims by adding the limitations wherein the cells are exposed to two or more electric fields, and wherein the Tm changes in a single direction away from the starting Tm. Applicant argues that this form of Tm change is not disclosed or suggested by any of the prior art of record. However, the Jacobs reference teaches that the cells were stimulated with a 1 second long train, or “burst” of 30 current pulses, thus meeting the limitation wherein a series of two or more electric fields are applied. Additionally, it is an expected property of the Tm to change in a single direction away from the starting Tm. In the hippocampal cells taught in Jacobs, the Tm of the cells, in response to the burst pulse would rise from the resting Tm (expected to be slightly positive of the potassium equilibrium potential) to the sodium equilibrium potential (i.e. a Tm change in a single direction), and then back towards the potassium equilibrium potential as the sodium channels inactivated. Claim 50 is unpatentable because the burst pulse electric field will maintain the Tm within the predefined range, if only for 1 second. Thus the claims are still unpatentable.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272-0871.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
April 13, 2004


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